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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 04/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/824,632	KUMAR ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This Application, filed April 14, 2004, does not claim priority to any copending application.

Claims 1-8 are pending.

Election/Restrictions

Claim 8 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 7, 2005.

Applicant's election without traverse of Invention I, claims 1-7, drawn to a non-human mammal comprising a disruption of IEX-1 in its genome, wherein said mammal has a higher blood pressure level than a control mammal lacking an IEX-1 disruption, in the reply filed on February 7, 2005 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic, homozygous mouse whose somatic and germ cells comprise a disruption in the IEX-1 locus of its genome, wherein the mouse exhibits blood pressure that is higher than a mouse that does not have a disruption in IEX-1 in its genome and expresses no IEX-1 protein, and a transgenic,

heterozygous mouse whose somatic and germ cells comprise a disruption in the IEX-1 locus of the genome, wherein breeding said transgenic heterozygous mice result in a transgenic, homozygous mouse whose somatic and germ cells comprise a disruption in the IEX-1 locus of its genome, wherein the mouse exhibits blood pressure that is higher than a mouse that does not have a disruption in IEX-1 in its genome and expresses no IEX-1 protein, does not reasonably provide enablement for any non-human mammal or any heterozygous non-human mammal comprising a disruption of the IEX-1 locus in its genome, wherein the mammal exhibits blood pressure that is higher than a control mammal that does not comprise the disruption. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is a mouse comprised of a disruption in IEX-1 of its genome, wherein the mouse exhibits higher blood pressure than a mouse with no disruption of IEX-1.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many

factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Claims 1, 3-7 broadly encompass any non-human mammal comprising a disruption of IEX-1 in its genome. However, at the time of filing, the art teaches that targeted gene disruptions were only known for mice. This is because the isolation of ES cells has only been demonstrated for mouse. Further, mice are the only mammals in which ES cells can be generated and which chimerism from ES cells extend to the germline. According to Murray, et al. (1999, *Transgenic Animals in Agriculture*, CAB International: Oxon, pages 58-61), the isolation of ES cells has not been accomplished unequivocally in other species, including in domestic livestock (Murray, et al., page 59, lines 3-4)." It is possible that putative ES cells have been isolated in other animals aside from the mouse. These include sheep, hamster, pig, cattle, mink, rabbit, rat, monkey and goat. However, in many cases the data characterizing them do not provide the most convincing data (Murray, et al., page 59, lines 10-17). Part of the discrepancy stemmed from the fact that scientists were relying on morphological comparisons of mouse ES cells to define what other animals' ES cells should look like. Some scientists added a second level of stringency, identifying ES cells by the fact that they differentiate

in vitro. However, the best level of stringency that identifies an ES cells is that the cells can differentiate *in vivo* (Murray, et al., page 60, second paragraph). In the case where chimeric offspring have been obtained after injection of putative ES cells into blastocysts, the species include mouse, pig, and rabbit (Murray, et al., page 59, lines 18-22). With regards to chimerism from ES cells extending to the germline, the only species in which this has been demonstrated is the mouse (Murray, et al., page 60, second paragragh, lines 19-22). Thus, the art teaches that making transgenic animals via ES cells is limited to mice. The specification does not teach how to obtain other mammalian ES cells. For this reason, a skilled artisan is not enabled for other transgenic mammals made from ES cells. In order for a skilled artisan to practice the claimed invention using the broad scope of any non-human mammal, a skilled artisan would first need to isolate and identify ES cells for other species of mammals. This is undue experimentation, as illustrated above by Murray, et al.

Claims 1-6 broadly encompass heterozygous non-human mammals comprising a disruption of IEX-1, wherein the heterozygous non-human mammal exhibits a higher blood pressure than that of a control animal. The specification, at the time of filing, teaches the characteristics of homozygous mice. However, no teachings were provided for the heterozygous mice. It is unclear if they also exhibited high blood pressure like the homozygous mice.

Claims 1-7 encompass transgenic mice comprised of an exogenous expression construct comprising a promoter, operatively linked to a nucleic acid sequence encoding any species of IEX-1, wherein the nucleic acid sequence encoding IEX-1 comprises a

disruption. While the claims encompass these mice, the specification does not provide guidance to an artisan as to how to make and use mice comprising such construct. At the time of filing, the art teaches that making transgenic non-human mammals is unpredictable. Mullins and Mullins (1996, J. Clin. Invest., 97: 1557-1560) teach that making transgenic mammals by nuclear injection is unpredictable. One of the examples of why making transgenic mammal is unpredictable is because position effects may affect the expression of the transgene. Rather, one problem of unpredictability in generating a transgenic mammal stems from the fact that some transgenes integrate in the genome at places that affect its expression. In some cases, the transgene could insert in the genome and be silenced. In other cases, the transgene could be positioned near an enhancer and be expressed embryonically and then shut off after the developmental stage has been passed. The upshot of this unpredictability is that a skilled artisan would never know when or if one would ever generate a transgenic mammal, unless one were actually created. This is further supported by Mench (1999, Transgenic Animals in Agriculture, CAB International: Oxon, pages 251-268, page 259, bottom to page 260, 1st parag.) who teaches that "because there can be so much variation in the sites of gene insertion, the numbers of gene copies transferred, and gene expression, every transgenic animal produced using microinjection is (theoretically, at least) unique in terms of its phenotype." Nothing in the specification teaches how to eliminate the issue of unpredictability, such that one could reliably obtain transgenic mammal. Further, while one could identify a transgenic animal using Southern blot analysis, the specification does not teach how to select for animals

express the transgene at levels that are assayable, nor does the specification teach what assays to use for these transgenic mammals comprising exogenous IEX-1, wherein the sequence of IEX-1 is comprised of any disruption. The criteria for transgenic animal selection depends on the transgene and depends on the biological function that one would assay. This would need to be empirically determined. For this reason, the specification does not enable a skilled artisan to make any transgenic mouse in the method encompassed by the claims.

Thus, for the reasons described above, the specification at the time of filing, provides teachings that enable an artisan to make and use a transgenic, homozygous mouse whose somatic and germ cells comprise a disruption in the IEX-1 locus of its genome, wherein the mouse exhibits blood pressure that is higher than a mouse that does not have a disruption in IEX-1 in its genome and expresses no IEX-1 protein and a heterozygous mouse, wherein breeding transgenic heterzygous mice result in a transgenic homozygous mouse whose somatic and germ cells comprise a disruption in the IEX-1 locus of its genome, wherein the mouse exhibits blood pressure that is higher than a mouse that does not have a disruption in IEX-1 in its genome and expresses no IEX-1 protein. However, the specification does not provide enablement commensurate with the full scope of the claims, as described above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Keulenaer et al. (2002, Circ. Res. 90:690-696) in view of Capecchi (1989, Trends in Genetics, 5: 70-76).

The claimed invention is a mouse comprised of a disruption in IEX-1 of its genome, wherein the mouse exhibits higher blood pressure than a mouse with no disruption of IEX-1.

De Keulenaer et al. teach that the IEX-1 gene is activated during the early response of a cardiomyocyte to mechanical stress and that the gene product inhibits hypertrophy without affecting cardiomyocyte viability. De Keulenaer et al. designed two adenoviral vectors wherein one expressed GFP (GFP-Ad) and the other expressed GFP and *iex-1* (IEX-Ad) (De Keulenaer et al., page 693, 2nd col., 2nd parag.). Cultured cardiomyocytes were infected with either of these vectors. De Keulenaer et al. teach that nearly 99% of the cardiomyocytes were infected with the viral construct and in the case where the cells were infected with IEX-Ad, the cells showed a 3-5 fold increase in IEX-1 levels. When cells were introduced to mechanical strain, cells infected with GFP-Ad were significantly enlarged and were hypertrophic. Cells that overexpress IEX-1 did not exhibit any hypertrophy (De Keulenaer et al., page 693, 2nd col., 2nd parag., lines 10-15). Further, De Keulenaer et al. teach that cells infected with GFP-Ad had significantly

increased rates of ^{3}[H]leucine uptake, while cells infected with IEX-Ad did not, indicating that IEX-1 had a negative regulatory effect on hypertrophic growth (De Keulenaer et al., page 693, 2nd col., 2nd parag. lines 15-22). While De Keulenaer et al. teach that IEX-1 can blunt the cardiomyocyte responses to mechanical strain, they do not teach how to make a transgenic mouse comprising a loss of function in IEX-1, wherein the animal is a model for hypertrophy.

Capecchi teaches mice comprising a disruption of a gene of interest and methods of making the mice by homologous recombination in mouse ES cells and introducing a disruption that prevents production of a functional protein (page 70, col. 2, parag. 1, lines 1-7) and (page 72, col. 1, parag. 3 to col. 2, parag. 1). Figure 1, page 71, teaches the isolation of mouse ES cells. Figure 2, page 72 teaches the production of germ line chimeras by inserting an ES cell into a mouse blastocyst and transferring the blastocyst to a surrogate mother mouse. Capecchi provides a specific example of disrupting the hprt gene in mouse ES cells (page 72, col.2, parag. 3 to page 73, col. 1, lines 1-9). Capecchi teaches a targeting vector and ES cells disrupted by the targeting vector (page 73, figure 3) and introduction of the targeting vector into mouse ES cells (page 72, col. 2, parag. 4, lines 1-4). Cappechi demonstrates that certain targeting vectors (page 75, figure 5) are used to target a specific gene by homologous recombination. Drug selection markers monitor whether vector integration was random or targeted. Capecchi provides motivation in stating the generation of specific mouse mutants by homologous recombination to induce a disruption in a gene of interest would

provide mouse models of disease mediated by the disrupted gene (page 75, col. 1, parag. 2, lines 1-7).

According to the American Heritage online dictionary, hypertrophy is "a nontumorous enlargement of an organ or a tissue as a result of an increase in the size rather than the number of constituent cells: *muscle hypertrophy.*" Keulaenaer, et al., teach that there is a hypertrophic response following mechanical strain. This means that following mechanical strain, the size of cardiomyocytes would increase in size. If the cardiomyocytes increased in size, then the diameter of the blood vessel would decrease. If the blood vessel diameter decreased, there would then be more mechanical strain to pump blood into tissues. More mechanical strain would then lead to an even more narrow blood vessel diameter. If this is the case, then an increase in blood pressure would be the outcome in this scenario. Ultimately, then, it could be conceived that a transgenic mouse comprising a disruption in IEX-1 could have blood pressures 5, 10, 20, or 30 mm of Hg above that of a mouse with no disruption in IEX-1.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to make a mouse comprising a disruption in IEX-1 in its genome, wherein the mouse exhibits high blood pressure as a result of cardiomyocyte hypertrophy.

There would have been a reasonable expectation of success given the results of De Keulenaer et al. for teaching that cardiomyocytes infected with IEX-1-Ad (adenovirus comprised of a nucleic acid sequence encoding IEX-1) do not exhibit hypertrophic response upon mechanical stimulation, while cardiomyocytes infected with GFP-Ad

(adenovirus comprised of a nucleic acid sequence encoding GFP) exhibit hypertropic response following mechanical stimulation and the teachings of Capecchi, wherein Capecchi teaches how to make targeting constructs and that disruption of a gene of interest would provide mouse models of disease mediated by the disrupted gene. Further, Capecchi provides motivation by teaching that the generation of specific mouse mutants by homologous recombination to induce a disruption in a gene of interest would provide mouse models of disease mediated by the disrupted gene.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH

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SUPERVISORY PATENT EXAMINER